09/095,565

EXHIBIT B

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
In re patent application of inventors Ketner et al.
Serial No. 09/904,698 Group Art Unit: 4755
Filed: 07/13/01 Examiner: Hill

For: ***"USE OF GENE PRODUCT OF ADENOVIRUS EARLY REGION 4 ORF-6 TO INHIBIT REPAIR OF DOUBLE-STRAND BREAKS IN DNA"***

Attention: Examiner Myron Hill
FACSIMILE: 703-746-7439

Dear Examiner,

Further to our telephone conversation of September 5, 2003, I am FAXing to you a copy of the amendment that we filed for the above-referenced United States patent application on May 12, 2003. I enclose:

1) a copy of the amendment (7 pages);
2) a copy of the amendment transmittal letter (one page)
3) a copy of the original postcard (one page); and
4) a copy of the postcard date-stamped May 12, 2003 by the USPTO (one page).

Thus, including this cover letter, this entire transmission contains 11 pages.

It is my understanding that the copy was requested because the amendment cannot be located (is not in the file) at the USPTO. The stamped receipt indicates that the document was, however, received by the USPTO on May 12, 2003.

If we can be of further assistance, please do not hesitate to contact us.

Ruth E. Tyler-Cross, Ph.D.
Registered Patent Agent

I hereby certify that I am transmitting a copy of an amendment filed May 12, 2003 and supporting documentation for Application Serial No.: 09/904,698. The transmission, containing eleven (11) pages, is being FAXed to the U.S. Patent Office at 703-746-7439 on September 5, 2003.

Ruth E. Tyler-Cross
Reg. No. 45,922

Docket No. D3940CCSSaa In re: ✓ patent/___ trademark application of

Applicant(s) G. Kyriel et al. Hand Delivered

Serial No. 09/904,698 Date Filed 7-13-01

Papers filed herewith on 5-12-03

___ Fees $_____ Deposit Account No. (if applicable) _____
(_____ filing fee; _____ Assignment charge; _____ Extension of Time;
_____ issue fee/advance copies; _____ other_____)

✓ Amendment ___ Notice of Appeal ___ Appeal Brief

___ Sheets of ___ Drawings ___ Proposed Drawing Corrections (w/___ drawings)

___ Change of Address ___ Request for Extension of Time

___ Assignment ___ Recordation Form Cover Sheet

___ Information Disclosure Statement ___ PTO-1449 and associated art (___ docs.)

___ Priority Document(s) ___ Other _____

_____

_____

Docket No. 7394005Sca In re: ✓ patent/___ trademark application of

Applicant(s) G. Yoshioka et al. Hand Delivered

Serial No. 09/904,698 Date Filed 7-13-01

Papers filed herewith on 5-12-03

___ Fees $_____ Deposit Account No. (if applicable) _____
(_____ filing fee; _____ Assignment charge; _____ Extension of Time;
_____ issue fee/advance copies; _____ other_____)

✓ Amendment ___ Notice of Appeal ___ Appeal Brief

___ Sheets of ___ Drawings ___ Proposed Drawing Corrections (w/___ drawings)

___ Change of Address ___ Request for Extension of Time

___ Assignment ___ Recordation Form Cover Sheet

___ Information Disclosure Statement ___ PTO-1449 and associated art (___ docs.)

___ Priority Document(s) ___ Other _____

AMENDMENT TRANSMITTAL LETTER (Small Entity)

Applicant(s): **G. Ketner, et al.**

Docket No.	Serial No.	Filing Date	Examiner	Group Art Unit
03940055AA	09/904,698	7/13/01	Hill	4755

Invention: **USE OF GENE PRODUCT OF ADENOVIRUS EARLY REGION 4 ORF-6 TO INHIBIT REPAIR OF DOUBLE-STRAND BREAKS IN DNA**

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

Transmitted herewith is an amendment in the above-identified application.

- ☐ Small Entity status of this application has been established under 37 CFR 1.27 by a verified statement previously submitted.
- ☐ A verified statement to establish Small Entity status under 37 FR 1.27 is enclosed.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST # PREV. PAID FOR		NUMBER EXTRA CLAIMS PRESENT		RATE	ADDITIONAL FEE
TOTAL CLAIMS	13	-	20	=	0	x	$9.00	$0.00
INDEP. CLAIMS	7	-	8	=	0	x	$42.00	$0.00
Multiple Dependent Claims (check if applicable) ☐								$0.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT								$0.00

- ☒ No additional fee is required for amendment.
- ☐ Please charge Deposit Account No. _____ in the amount of _____
  A duplicate copy of this sheet is enclosed.
- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. **50-2041**
  A duplicate copy of this sheet is enclosed.
  - ☒ Any additional filing fees required under 37 C.F.R. 1.16.
  - ☒ Any patent application processing fees under 37 CFR 1.17.

Dated: **May 12, 2003**

Signature

Ruth Tyler-Cross
Reg No. 45,922
Whitham, Curtis & Christofferson, P.C.
11491 Sunset Hills Road, Suite 340
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703-787-9400

30743
PATENT TRADEMARK OFFICE

I certify that this document and fee is being deposited on _____ with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

HAND DELIVERED

Typed or Printed Name of Person Mailing Correspondence

cc:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of inventors Ketner et al.

Serial No. 09/904,698
Filed: 07/13/01

Group Art Unit: 4755
Examiner: Hill

For: ***"USE OF GENE PRODUCT OF ADENOVIRUS EARLY REGION 4 ORF-6 TO INHIBIT REPAIR OF DOUBLE-STRAND BREAKS IN DNA"***

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action mailed on 02/11/2003, please amend the above-identified patent application as follows:

IN THE CLAIMS:

Please amend claims 6 and 12-15, an edited copy of which follows and a clean copy of which is attached as Appendix A.

Claim 6 (twice amended). A method of inhibiting repair of <u>double-stranded</u> breaks in [double-stranded] DNA in a cell which comprises introducing into the cell [the gene product of the] <u>DNA containing</u> early region 4 (E4) open reading frame 6 (ORF6) <u>and E1B region</u> of genomic adenoviral DNA.

Claim 12 (twice amended). A method [of increasing efficiency of] <u>for</u> chemotherapeutic or

radiation treatment of cancer in a subject while inhibiting repair of double-stranded breaks in DNA in cancer cells in said subject which comprises: a) introducing into said cancer cells [of the subject the gene product of the] DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA, in a quantity sufficient to inhibit repair of double-stranded breaks in DNA in said cancer cells and b) administering a chemotherapeutic agent or radiation to the subject.

13 (twice amended). The method of claim 12, wherein the [gene product of the] DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells before the chemotherapeutic agent or radiation is administered to the subject.

14 (twice amended). The method of claim 12, wherein the [gene product of the] DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells after the chemotherapeutic agent or radiation is administered to the subject.

15 (twice amended). The method of claim 12, wherein the [gene product of the] DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells concurrently with administering the chemotherapeutic agent or radiation is administered to the subject.

REMARKS

Claims 6-18 are pending in the application. Claims 6 and 12-16 are under consideration, claims 7-11, 17 and 18 having been withdrawn from consideration as the result of a restriction requirement. By this amendment, claims 6 and 12-15 have been amended.

35 U.S.C. § 112, second paragraph rejection

Claims 6 and 12-16 stand rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Examiner states that it is not clear in the method what is being introduced into the cell or what is intended to be introduced into the cell, the gene (nucleic acid) or the gene product (protein). For the present Office Action, the Examiner has assumed that the gene is introduced and the gene product expressed from the gene *in vivo*.

Claims 6 and 12-15 have hereby been amended to recite that it is DNA containing the relevant encoding sequences that is introduced into the cell. Applicant submits that this amendment does not introduce new matter since, for example, on page 25 at lines 33-36 of the specification two exemplary methods of introducing the gene product are given (via a plasmid and via an adenoviral vector), both of which involve introducing DNA into the cell.

Claim 6 has further been amended to recite that it is the "repair of double-stranded breaks in DNA" that is corrected rather than the "repair of breaks in double-stranded DNA". Applicant submits that other types of breaks can occur in double-stranded DNA (e.g. single strand breaks) but that the subject matter of the present invention is accurately described as the repair of double-stranded breaks in DNA. The previous error was inadvertently introduced in the last amendment to claim 6. Support for the present form of claim 6 is found in the specification, for example, at page 22, lines 10-11. Thus, this amendment does not introduce new matter.

Examiner further asserts that it is not clear in claims 12-16 what is meant by "increasing efficiency" of the agent.

Claim 12 has hereby been amended to eliminate the phrase "increasing efficiency". Claim 12 has been amended to recite that the method is a method for chemotherapeutic or radiation treatment of cancer in a subject while inhibiting repair of breaks in double strand DNA in cancer cells in the subject. Support for the claim is found in the specification, for example on page 43, lines 8-12. Radiation and chemotherapy treatments are known to induce double strand breaks in cellular DNA, resulting in cell death, unless repair of the breaks occurs. The agent of the present invention has been shown to prevent repair of double strand breaks in cells (see, for example,

page 43, lines 27-30; page 76, lines 19-21). Thus, the amendments do not constitute new matter.

35 U.S.C. § 112, first paragraph rejection

Claims 12-16 stand rejected under 35 U.S.C.§ 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Examiner states that chemotherapeutic agents and radiation therapies are a very unpredictable area, that the method would require targeting of the cancer cells, and that, due to the wide range of cancers, the unpredictability in the art, and the lack of specific examples, it would require undue experimentation to use the invention as claimed.

Applicant respectfully disagrees. Examiner has recognized the description of the method of claims 12-16 in the paragraph on page 42, beginning at line 29. Applicant submits that the paragraph, in conjunction with knowledge extant in the field, gives ample guidance for the use of the adenoviral vector of the present invention for increasing efficiency of chemotherapeutic or radiation treatment of cancer cells, via inhibiting the repair of double-stranded breaks in DNA in the cancer cells.

Applicant submits that the field of gene therapy has progressed significantly and that a body of literature which provides guidance to those in the field exists. Skilled artisans, such as physicians experienced in gene therapy, would recognize that the delivery of genetic material via adenoviruses to cells in general, and to cancer cells in particular, is well-known, and will be aware of the various alternatives available for carrying out delivery of the adenovirus. For example, Khuri et al. and Schuler et al. (described above) both describe the use of adenoviral vectors in conjunction with radiation or chemotherapy to improve the results of the cancer therapy. Further, modifications to an adenoviral vector such as those described in the present invention would not interfere with delivery of the adenovirus or the pattern of gene expression described in amended claims 6 and 12, as many versions of adenoviral vectors are known and have been successfully used to transfect cells *in vivo*.

The "experimental" aspect of the present invention is the discovery of which genes are beneficial to express for the purpose of inhibiting the repair of double-stranded breaks in DNA.

Thus, one skilled in the art would require no more explicit teaching than that which is found in the present application, coupled with the knowledge in the field at the time the present application was filed, in order to successfully practice the present invention as recited in claims 12-16.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

35 U.S.C. §102 (b) rejection

Claim 6 stands rejected under 35 U.S.C. §102 (b) as anticipated by Ramalingam et al.. Examiner states that Ramalingam et al. discloses an adenovirus that expresses E4 orf 6 (column 2, second full paragraph). Examiner states that while Ramalingam is silent on the effect of E4ORF6, the method involves the same step of introducing into the cell the gene product of E4ORF6 by way of adenovirus infection.

Claim 6 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cell in order to inhibit repair of double-stranded breaks in DNA in the cell. Support for this amendment is found in the specification at page 21, lines 16-19, and on page 25, lines 17-19, both of which locations state that in some embodiments of the invention, both E4 orf6 and region E1B are utilized. Applicant submits that this amendment therefore does not introduce new matter.

Ramalingam et al. utilize adenoviral gene transfer vectors in which the E4 region is present but in which the E1 region is absent. Therefore, the work described by Ramalingam et al. does not anticipate claim 6 as amended, which requires the presence of both E4 orf6 and region E1B.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

35 U.S.C. §102 (a) rejection

Claims 6 and 12-16 stand rejected under 35 U.S.C. §102 (a) as anticipated by Vollmer. Examiner states that Vollmer discloses a method of improving the efficiency of chemotherapeutic agents with adenovirus E4 orf 6 in mice, and that while Vollmer is silent on E4

orf 6, the virus was grown on 293 cells which only complement E1 mutant adenoviruses and therefore the virus must have E4 orf 6.

Claim 6 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cell in order to inhibit repair of double-stranded breaks in DNA in the cell. Claim 12 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cancer cell in order to inhibit repair of double-stranded breaks in DNA in the cell caused by chemo- or radiation therapy. Support for these amendments is as discussed above. The work of Vollmer et al. was carried out with a construct containing all of the adenoviral genome except E1B. Therefore, Vollmer et al. do not anticipate the subject matter of claims 6 and 12 (and thus dependent claims 13-16) as amended since claims 6 and 12 now recite the presence of both E4 orf6 and region E1B.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

Formal Matters and Conclusion

In view of the foregoing, Applicant submits that all rejections have been successfully traversed. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

Please charge any underpayment or credit any overpayment of fees to attorney's deposit account # 50-2041.

Respectfully submitted,

Ruth E. Tyler-Cross

Reg. No. 45,922

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Appendix A: Clean Copy of Amended Claims

Claim 6. A method of inhibiting repair of double-stranded breaks in DNA in a cell which comprises introducing into the cell DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA.

Claim 12. A method for chemotherapeutic or radiation treatment of cancer in a subject while inhibiting repair of double-stranded breaks in DNA in cancer cells in said subject which comprises: a) introducing into said cancer cells DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA, in a quantity sufficient to inhibit repair of double-stranded breaks in DNA in said cancer cells and b) administering a chemotherapeutic agent or radiation to the subject.

13. The method of claim 12, wherein the DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells before the chemotherapeutic agent or radiation is administered to the subject.

14. The method of claim 12, wherein the DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells after the chemotherapeutic agent or radiation is administered to the subject.

15. The method of claim 12, wherein the DNA containing early region 4 (E4) open reading frame 6 (ORF6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells concurrently with administering the chemotherapeutic agent or radiation is administered to the subject.